This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) A mixed sequence oligonucleotide comprising at least 12 nucleotides in length and having a 3' end and a 5' end and divided into a first portion and a further portion,

said first portion ~~being capable of~~ comprising nucleotides that support cleavage of a complementary target RNA by human RNase H1 polypeptide,

said further portion ~~being incapable of supporting~~ comprising nucleotides that do not support said cleavage by said RNase H1

wherein said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide.

Claims 2 to 28 Cancelled

29. (currently amended) A mixed sequence oligonucleotide comprising at least 12 nucleotides and having a 3' end and a 5' end and divided into a first portion and a further portion,

said first portion supports cleavage of a complementary target RNA by a purified or isolated human RNase H1 polypeptide,

said further portion does not support said cleavage by said purified or isolated RNase H1 and where

said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide.

30. (previously presented) The oligonucleotide of claim 29 comprising from about 12 to about 50 nucleotides.

31. (previously presented) The oligonucleotide of claim 29 comprising from about 12 to about 25 nucleotides.

32. (currently amended) A mixed sequence oligonucleotide comprising at least 12 nucleotides and having a 3' end and a 5' end and divided into a first portion and a further portion,

said first portion supports cleavage of a complementary target RNA by human RNase H1 polypeptide,

said further portion does not support said cleavage by said RNase H1;

wherein:

said first portion comprises at least 6 nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide;

~~each of~~ said nucleotides of said first portion have B-form conformational geometry and are joined together in a continuous sequence, and

at least one of said nucleotides having B-form conformational geometry is not a 2'-deoxyribonucleotide.

33. (currently amended) A mixed sequence oligonucleotide comprising at least 12 nucleotides and having a 3' end and a 5' end and divided into a first portion and a further portion,

said first portion supports cleavage of a complementary target RNA by human RNase H1 polypeptide,

said further portion does not support said cleavage by said RNase H1;

wherein:

said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide; and

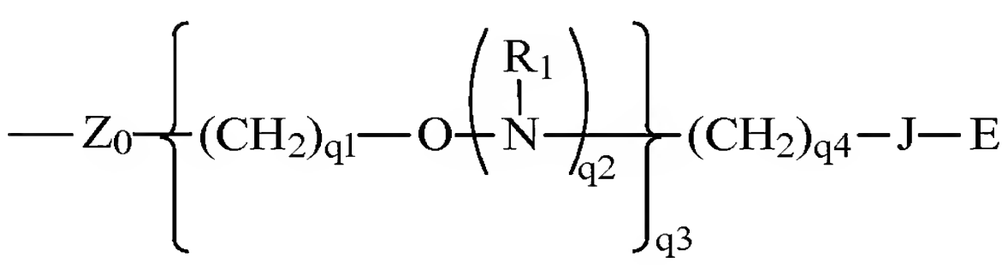
each of said nucleotides of said first portion is, independently, a 2'-SCH_3 ribonucleotide, a 2'-NH_2 ribonucleotide, a 2'-$NH(C_1$-C_2 alkyl) ribonucleotide, a 2'-$N(C_1$-C_2 alkyl)$_2$ ribonucleotide, a 2'-CF_3 ribonucleotide, a 2'=CH_2 ribonucleotide, a 2'=CHF ribonucleotide, a 2'=CF_2 ribonucleotide, a 2'-CH_3 ribonucleotide, a 2'-C_2H_5 ribonucleotide, a 2'-CH=CH_2 ribonucleotide or a 2'-C/CH ribonucleotide.

34. (previously presented) The oligonucleotide of claim 29 wherein at least one of said nucleotides of said first portion is a 2'-deoxyribonucleotide.

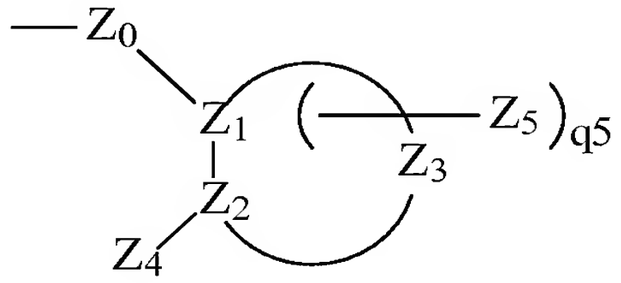
35. (previously presented) The oligonucleotide of claim 29 wherein said nucleotides of said first portion are joined together in said continuous sequence by phosphorothioate linkages.

36. (currently amended) The oligonucleotide of claim 29 wherein said further portion includes a plurality of nucleotides, at least some of said nucleotides comprise a 2' substituent group wherein each substituent group is, independently, hydroxyl, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, amino, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, O-alkenyl, O-alkynyl, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or each substituent group has one of formula I or II:



I



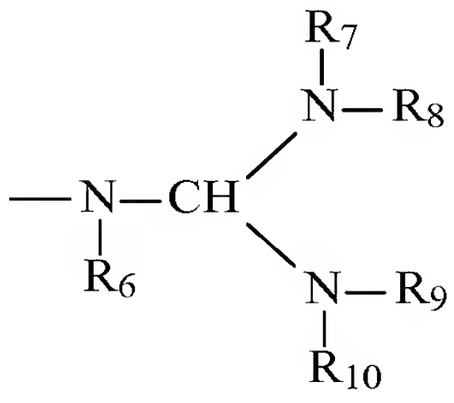
II

wherein:

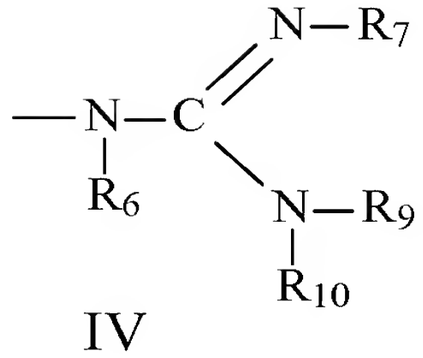
Z_0 is O, S or NH;

J is a single bond, O or C(=O);

E is C_1-C_{10} alkyl, $N(R_1)(R_2)$, $N=C(R_1)(R_2)$, or has one of formula III or IV;



III



IV

each R_6, R_7, R_8, R_9 and R_{10} is, independently, hydrogen, $C(O)R_{11}$, substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl, substituted or unsubstituted C_2-C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_7 and R_8, together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R_9 and R_{10}, together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{11} is, independently, substituted or unsubstituted C_1-C_{10} alkyl, trifluoromethyl, cyanoethyloxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

each R_1 and R_2 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl, substituted or unsubstituted C_2-C_{10} alkynyl, wherein said substitution is OR_3, SR_3, NH_3^+, $N(R_3)(R_4)$, guanidino or acyl where said acyl is an acid amide or an ester;

or R_1 and R_2, together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R_1, T and L, together, are a chemical functional group;

each R_3 and R_4 is, independently, H, C_1-C_{10} alkyl, a nitrogen protecting group, or R_3 and R_4, together, are a nitrogen protecting group;

or R_3 and R_4 are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C(=NH)N(H)R_5, C(=O)N(H)R_5 or OC(=O)N(H)R_5;

R_5 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(R_1)(R_2) OR_1, halo, SR_1 or CN;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10; and

q_5 is [[from]] 0, 1 or 2;

provided that when q_3 is 0, q_4 is greater than 1.

37. (currently amended) The oligonucleotide of claim 29 wherein <u>said further portion comprises a plurality of nucleotides and wherein</u> each of said nucleotides of said further portion is, independently, a 2'-F ribonucleotide, a 2'-O-(C_1-C_6 alkyl) ribonucleotide, or a 2'-O-(C_1-C_6 substituted alkyl) ribonucleotide wherein the substitution is C_1-C_6 ether, C_1-C_6 thioether, amino, amino(C_1-C_6 alkyl) or amino(C_1-C_6 alkyl)$_2$.

38. Cancelled

39. (currently amended) The oligonucleotide of claim 29 wherein <u>said further portion comprises a plurality of nucleotides and wherein</u> at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said first portion.

40. (currently amended) The oligonucleotide of claim 29 wherein said further portion comprises a plurality of nucleotides and wherein at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 5' to said first portion.

41. (currently amended) The oligonucleotide of claim 29 wherein said further portion comprises a plurality of nucleotides and wherein at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said first portion and at least two of said further portion are joined together in a continuous sequence that is positioned 5' to said first portion.

42. (currently amended) The oligonucleotide of claim 29 wherein said further portion comprises a plurality of nucleotides and wherein at least four of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said first portion.

43. (currently amended) The oligonucleotide of claim 29 wherein said further portion comprises a plurality of nucleotides and wherein at least four of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 5' to said first portion.

44. (currently amended) The oligonucleotide of claim 29 wherein said further portion comprises a plurality of nucleotides and wherein at least four of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said first portion and at least four of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 5' to said first portion.

45. (withdrawn) A mixed sequence oligonucleotide comprising at least 8 oligonucleotides and having a 2'-OH arabinonucleotide sequence of at least 6 nucleotides and where at least one of said arabinonucleotides is positioned 8 to 12 nucleotides from the 3' end of said

oligonucleotide, and wherein said oligonucleotide supports cleavage of a complementary target RNA by human RNase H1 polypeptide.

46. (withdrawn) A mixed sequence oligonucleotide comprising at least 8 oligonucleotides and having a a 2'-F arabinonucleotide sequence of at least 6 nucleotides and where at least one of said 2'-F arabinonucleotides is positioned 8 to 12 nucleotides from the 3' end of said oligonucleotide, and wherein said oligonucleotide supports cleavage of a complementary target RNA by human RNase H1 polypeptide.

47. (withdrawn) A mixed sequence oligonucleotide comprising 8 to 25 nucleotides and having a 2'-OH arabinonucleotide sequence wherein at least one of the nucleotides of said sequence is positioned 8 to 12 nucleotides from the 3' end of said oligonucleotide, wherein said oligonucleotide supports cleavage of a complementary target RNA by human RNase H1 polypeptide.

48. (withdrawn) A mixed sequence oligonucleotide comprising 8 to 25 nucleotides and having a 2'-F arabinonucleotide sequence wherein at least one of the nucleotides of said sequence is positioned 8 to 12 nucleotides from the 3' end of said oligonucleotide, wherein said oligonucleotide supports cleavage of a complementary target RNA by human RNase H1 polypeptide.

49. (currently amended) A chimeric oligonucleotide comprising 8 to 25 nucleotides and having a portion that supports cleavage of a complementary target RNA by human RNase H1 polypeptide wherein said portion supporting said cleavage is at least 6 contiguous nucleotides in length and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is positioned 8 to 12 nucleotides from the 3' end of said oligonucleotide, wherein said oligonucleotide supports cleavage of a complementary target RNA by human RNase H1 polypeptide.

50. (previously presented) The oligonucleotide of claim 49 wherein said RNase H1 polypeptide is a purified or isolated polypeptide.

51. (withdrawn) A method comprising contacting an oligonucleotide according to claim 29 with RNA or DNA *in vitro*.

52. (withdrawn) A method comprising contacting an oligonucleotide according to claim 32 with RNA or DNA *in vitro*.

53. (withdrawn) A method comprising contacting an oligonucleotide according to claim 33 with RNA or DNA *in vitro*.

54. (withdrawn) A method comprising contacting an oligonucleotide according to claim 45 with RNA or DNA *in vitro*.

55. (withdrawn) A method comprising contacting an oligonucleotide according to claim 46 with RNA or DNA *in vitro*.

56. (withdrawn) A method comprising contacting an oligonucleotide according to claim 47 with RNA or DNA *in vitro*.

57. (withdrawn) A method comprising contacting an oligonucleotide according to claim 48 with RNA or DNA *in vitro*.

58. (withdrawn) A method comprising contacting an oligonucleotide according to claim 29 with RNA or DNA in a cellular assay.

59. (withdrawn) A method comprising contacting an oligonucleotide according to claim 32 with RNA or DNA in a cellular assay.

60. (withdrawn) A method comprising contacting an oligonucleotide according to claim 33 with RNA or DNA in a cellular assay.

61. (withdrawn) A method comprising contacting an oligonucleotide according to claim 45 with RNA or DNA in a cellular assay.

62. (withdrawn) A method comprising contacting an oligonucleotide according to claim 46 with RNA or DNA in a cellular assay.

63. (withdrawn) A method comprising contacting an oligonucleotide according to claim 47 with RNA or DNA in a cellular assay.

64. (withdrawn) A method comprising contacting an oligonucleotide according to claim 48 with RNA or DNA in a cellular assay.

65. (withdrawn) A method comprising contacting an oligonucleotide according to claim 49 with RNA or DNA *in vitro*.

66. (withdrawn) A method comprising contacting an oligonucleotide according to claim 49 with RNA or DNA in a cellular assay.

67. (withdrawn) A method comprising contacting an oligonucleotide according to claim 50 with RNA or DNA *in vitro*.

68. (withdrawn) A method comprising contacting an oligonucleotide according to claim 50 with RNA or DNA in a cellular assay.

69. (withdrawn) A method comprising:

selecting a parameter associated with interaction of an oligonucleotide, a target nucleic acid and human RNase H1 polypeptide,

selecting a cell containing human RNase H1 polypeptide and a target nucleic acid,

selecting first and second oligonucleotides each having a sequence substantially commpementary to said target nucleic acid,

contacting said cell with said first oligonucleotide and measuring said parameter,

contacting said cell with said second oligonucleotide and measuring said parameter,

comparing measurements, and

using said comparison to select one of said first or said second oligonucleotides for modulating said target in the presence of said human RNase H1 polypeptide in said cell.

70. (withdrawn) The method of claim 69 wherein said parameter is one of site preference for cleavage, sequence preference for cleavage or processivity of cleavage.

71. (withdrawn) The method of claim 69 wherein said measurement is a measurement of at least one of K_d, K_{max}, K_m or K_{cat}.

72. (withdrawn) An oligonucleotide for modulating a target nucleic acid in the presence of human RNase H1 polypeptide wherein said oligonucleotide is identified using the process of claim 69.

73. (withdrawn) An optimized oligonucleotide for modulating a target nucleic acid wherein said optimized oligonucleotide is identified using the process of claim 69.

74. (withdrawn) The method of claim 69 further comprising:

selecting a further oligonucleotide,

contacting said cell with said further oligonucleotide and measuring said parameter,

comparing the measurement of this further oligonucleotide to that of said selected first or said second oligonucleotides and selecting one of said first, said second or said further oligonucleotide.